

February 8th, 2016

Project Title: Methenamine Hippurate versus Suppressive Antibiotics in the Prevention of Recurrent Urinary Tract Infections

NCT03077711

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Introduction: Recurrent urinary tract infections (UTIs) are common bacterial infections seen in women of all ages across disciplines. Several treatment options are now available for prevention, but the gold standard is considered to be suppressive antibiotics. Considering increasing antibiotic resistance in treating UTIs, we are looking for viable alternatives. There has not yet been a head-to-head comparison of the treatment options for the last 2 decades.

Hypothesis: Our hypothesis is that methenamine hippurate will have less or equal recurrences of UTI's as suppressive antibiotics and have a lower side effect profile.

Literature review:

Urinary tract infections (UTIs) are one of the most common bacterial infections in women and account for a significant number of office and emergency room visits per year¹⁻². UTIs can cause vomiting, pain, dysuria, septicemia, fever, fatigues, and occasionally renal failure in the worst cases. Elderly patients, long-term catheter use, or patients with renal disease are examples of those at high risk of repeated UTIs, and patients more likely to have serious complications³. The risk of recurrence has been shown to be between 20-30% after one infection⁴. One study by Ikaheimo showed that recurrent infections occurred in 44% of women presenting in a primary care setting that had been treated for UTI within the prior 12 months⁵.

Several methods are available for use in the prevention of recurrent urinary tract infections (UTIs). One review of management of recurrent UTIs stated that there is lacking evidence for cranberry, Vitamin C, and methenamine hippurate and concluded that antibiotic prophylaxis remains the most effective method of management¹. However, long-term use of antibiotics can lead to resistance, in addition nausea and candidiasis. Several antibiotics have been used in the prevention of recurrent UTIs including most commonly trimethoprim and nitrofurantoin. Trimethoprim can lead to Lyell's syndrome, Stevens-Johnson syndrome and pancytopenia. Even at low doses, long-term nitrofurantoin use may result in hepatotoxicity and pneumonitis, although usually reversible¹.

Methenamine hippurate is one such alternative that is currently used in practice. The last randomized control trial however comparing methenamine hippurate to suppressive antibiotics was in 1985. Earlier randomized control trials had promising results showing methenamine hippurate to be effective without long-term adverse effects. However, these studies had very small populations and did not follow patients for longer than 6 months to 1 year. The Cochrane review of the literature concluded that there is not enough evidence to support the use of methenamine hippurate for prevention of suppression of recurrent UTIs and encouraged large randomized trials to answer this question⁶. Methenamine hippurate may be a good alternative to suppressive antibiotics if it is as effective with a better adverse effect profile.

Primary Aim(s): Identify if there is a differential impact on prevention of recurrent UTIs when treated with either trimethoprim or methenamine hippurate in a 6 and 12 month period.

Secondary Aim(s):

1. Identify adverse reactions of study medications in each group.
2. Determine whether or not estrogen has a more additive effect to antibiotics or methenamine hippurate in post-menopausal women.
3. Identify tolerability of the study medications and whether the size of the pills or the frequency of taking them prevents patients from continuing therapy.

Methods:

This will be a prospective randomized control trial comparing the efficacy of methenamine hippurate versus trimethoprim, a suppressive antibiotic used in the prevention of recurrent UTIs. The definition of a UTI will include patients who have had symptoms including dysuria, suprapubic pain, increased frequency and urgency, malodorous urine, and hematuria plus a positive urine culture with any degree of bacteriuria.

Women with a diagnosis of recurrent UTIs, having had at least two UTIs in the past 6 months or 3 in the past year that are proven culture positive with symptoms, will be included in the study. Upon entry into the study, the patient must have been treated for their last infection and have a negative urine culture before enrollment. Women who have received previous prophylaxis for recurrent UTIs but have not taken it for a minimum of 30 days, will be eligible for enrollment. The patients will be prospectively followed for one year.

After a patient is diagnosed with recurrent UTIs, she will be evaluated with a repeat urine culture to confirm a negative prior to enrollment. Informed consent will then be obtained from the patient by the investigator or designate, who will then randomize the patient to prophylaxis with either methenamine hippurate or trimethoprim. The groups will be randomized in a 1:1, methenamine hippurate to trimethoprim. The randomization will be done by research coordinator and computer-generated sequence prior to the initiation of the study. Randomization will be provided in sequentially-numbered, sealed envelopes. Because estrogen is a known confounding factor, we will periodically assess the number of estrogen users in each arm at 3 month intervals. If there is a large discrepancy, we will adjust the randomization to include a stratification method assigned equal amounts of estrogen users to each arm moving forward. Most likely, randomization itself will control for the number of estrogen users in each group. Each envelope will remain sealed until inclusion and exclusion criteria are met and informed consent obtained. Patient identification including initials and date of birth, envelope numbers, and treatment designation will be recorded on the enrollment form.

This study will not include a placebo arm as it would be unethical to not treat a patient with recurrent UTIs, given known treatment. Our patients and investigators will not be blinded due to cost it would entail to blind the study medications. Investigators will have

to order the specific medication at the patient's requested pharmacy. Patients will have to know which medications they are picking up from the pharmacy. The two medications differ in frequency and size and would be difficult to blind the patient to. Investigators may choose to crossover to the opposing medication or add it to the patient's current regimen if she continues to have recurrences.

Inclusion:

1. age greater than 18-99
2. recurrent UTI: at least 2 in the past 6 months or 3 in past year (culture positive, any CFU/mL)
3. must have been symptomatic with dysuria, urgency, frequency, suprapubic pain, hematuria, malodorous urine
4. treated for last UTI and negative urine culture on entry into study
5. English speaking

Exclusion:

1. pregnancy
2. urinary tract abnormalities (eg kidney stones)
3. pyelonephritis
4. renal insufficiency or failure
5. known allergy to medications
6. prophylaxis for post-coital recurrent UTIs

Interventions: The groups will be randomized in a 1:1 of methenamine hippurate to trimethoprim once diagnosed with recurrent UTIs, inclusion and exclusion criteria are met, and patient consents to participate in study.

Outcomes**Primary:**

1. Time to subsequent infection
2. Number of patients infection-free after 6-12 months
3. Number of infections in 6-12 months per patient

Secondary:

1. Adverse effects of medications
2. Additive effect of estrogen
3. Patient tolerability of medications

Sample Size:

There are very few prior studies which compared methenamine hippurate to trimethoprim currently published. One randomized control trial from 1982 by Kasanen et al, allocated patients with recurrent UTIs to one of 4 groups: placebo, nitrofurantoin 75 mg, methenamine hippurate 1 gm, or trimethoprim 100 mg. At one year, 63.2% of those in the placebo group had a recurrence, compared to 34.2% in the methenamine hippurate group, 25% in the nitrofurantoin group, and 10.4% in the trimethoprim group⁷. In a Cochrane review by Aydin et al, current

prevention strategies were reviewed for the prevention of recurrent UTIs. Prophylactic antibiotics reduced the rate of recurrence to 0.4 UTIs/patient/year. A crossover study done by Cronberg et al found that the recurrence rate was reduced to 0.8 UTIs/patient/year using long term methenamine hippurate prophylaxis⁶. Based on the results of these prior studies, we performed a power and sample size calculation. It was determined that 41 subjects per arm would be required to detect the expected difference in response with 80% power at a 0.05 significance level. We predict a 30% attrition rate, and therefore determine that we should have 65 subjects per arm.

Proposed Analyses:

We will determine:

1. The time to subsequent UTI recurrence among patients with the diagnosis of recurrent UTIs under suppressive therapy with either methenamine hippurate or Trimethoprim. Differences in time to subsequent infection will be compared and assessed for statistical significance using a paired, two-tailed Student's t-test.
2. At 12 months, the percentage of patients enrolled to either arm that are infection-free. We will count patients who discontinued the study medications, added the opposing study medication, or crossed over to using the opposing study medication as failures and include them in the total number of patients in the denominator. The percentages will be compared using a one sample t-test.
3. The number of recurrences in each group at 12 month intervals. We will determine the rate of recurrences in each arm and compare them using a student's t-test.
4. The additive effect of estrogen will be determined at 12 months. A logistic regression model will be used to compare the two groups to determine if a combination of the study drug to estrogen further prevented recurrences in post-menopausal women.
5. The percentages of adverse effects of each of the study medications will be compared between the two groups using a one sample t-test.
6. Patient tolerability to the study medications. A tolerability survey will be administered at subsequent follow up visits to the enrollment into the study. Percentage of patients who discontinue the study medications will be compared between both groups using a one sample t-test.

References:

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